REMARKS

Consideration of this application in view of the above amendments and following remarks is respectfully requested. Claims 1-4, 19, and 20 are now pending. Claims 1-4 and 19 have been amended, and claim 21 has been added. Support for the amendment may be found throughout the claims and specification as originally filed. Specific support for monoclonal antibodies is provided throughout the specification, including Example 9, and specific support for antibody derivatives is provided, for example, in Table 2. This amendment is not to be construed as acquiescence to any rejection and is made without prejudice to prosecution of any subject matter modified by the amendment in a related divisional, continuation, or continuation-in-part application.

Rejection Under 35 U.S.C. § 101

Claims 1-4 and 19 stand rejected under 35 U.S.C. §101, as allegedly directed to non-statutory subject matter. More specifically, the Examiner objects to claimed antibodies as being products of nature.

Applicants respectfully traverse this basis of rejection and submit that the claims are directed to statutory subject matter. Applicants note that claim 1 has been amended to recite "an isolated growth blocking agent," as suggested by the Examiner. Applicants submit that an isolated growth blocking agent is not a product of nature. In addition, Applicants submit that the claimed isolated growth blocking agent, directed to TcII and capable of inhibiting cellular uptake of vitamin B12, possesses specific and substantial utility as compared to a non-isolated growth blocking agent directed to TcII, including, for example, being useful as a pharmaceutical agent to treat both malignant and non-malignant disease, as described throughout the specification, such as, for example, on page 24, lines 19-35 and in Examples 2-4.

Applicants submit that the rejection under 35 U.S.C. § 101 has been obviated in light of the amendment and remarks set forth above. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-4 and 19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More specifically, the Action alleges that the specification fails to provide any written description of any growth blocking agent directed to a vitamin B_{12} binding site on TcII, which is capable of competitively antagonizing or modulating said binding site to inhibit the cellular uptake of vitamin B12.

Applicants respectfully traverse this basis of rejection and submit that the specification provides adequate written description to support the claimed genus of growth blocking agents. As an initial matter, Applicants disagree with the Action's conclusion that specification fails to provide any written description of a growth blocking agent directed to a vitamin B_{12} binding site on TcII, which is capable of competitively antagonizing or modulating said binding site to inhibit the cellular uptake of vitamin B12. Applicants submit that the specification describes, for example, monoclonal antibodies against TcII that inhibit binding of vitamin B12 to TcII (Example 9 and Figure 5) and inhibit cellular uptake of vitamin B12 (Example 10 and Figure 6), including, for example, hybridomas 2-2, 3-11 and 4-7 (page 17, lines 32-33). Furthermore, Applicants submit that the skilled artisan would understand that such antibodies, since they physically interfere with vitamin B_{12} binding to TcII, are almost certainly directed to at least a portion of the vitamin B_{12} binding site on TcII. Nonetheless, Applicants note that claim 1, as amended, does not require that the antibody is directed to any specific site on TcII. Accordingly, adequate written description of a claimed growth blocking agent is provided by the description of these monoclonal antibodies.

Furthermore, Applicants note that under the Examination Guidelines set forth by the Patent and Trademark Office, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, at 1106. Applicants further note that both structural and functional properties may serve as sufficient identifying characteristics in the context of meeting the written description requirement of 35 U.S.C. § 112. *Id.* Applicants

respectfully submit that the instant specification provides sufficient identifying characteristics to demonstrate to the skilled artisan that Applicants were in possession of the claimed invention at the time of filing the application. Applicants have provide at least two distinct and readily ascertainable functional characteristics by which the skilled artisan can easily recognize a claimed growth blocking agent. One identifying characteristic is that the agent is directed to TcII, and a second characteristic is that the agent is capable of inhibiting the cellular uptake of vitamin B_{12}. Applicants further note that the skilled artisan may readily determine whether a compound possesses these characteristics, particularly in light of the guidance provided by the instant specification, which describes routine procedures for determining if a compound is directed to TcII and inhibits cellular uptake of vitamin B_{12} (See, *e.g.*, page 18, line 25, to page 19, line 6, and Example 10). Accordingly, Applicants submit that the written description requirement is satisfied for the claimed compounds and respectfully request that this basis of rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-4 and 19 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that it would require undue experimentation to make and use the claimed growth blocking agents.

Applicants respectfully traverse this basis of rejection and submit that the specification adequately teaches the skilled artisan how to make and use the claimed invention. Applicants submit that the specification provides detailed guidance regarding the production of claimed compounds, including, *e.g.*, monoclonal antibodies directed against TcII that inhibit binding and cellular uptake of vitamin B_{12} (pages 9-17 and Examples 8-10). In addition, the specification provides detailed procedures for screening compounds, including polypeptides and small organic molecules, to identify those possessing the claimed characteristics. For example, page 10, lines 4-8, describes methods of screening antibodies, and page 17, lines 3-25 describes methods of screening small organic molecules to identify those that inhibit vitamin B12 binding and uptake. In addition, successful working examples of methods of producing and screening compounds are provided in Examples 8-12.

Applicants further submit that the production and screening of growth blocking agents directed to TcII and capable of inhibiting cellular uptake of vitamin B_{12} would require merely routine methods and assays and is, therefore, fully enabled by the instant specification. As repeatedly stated by the Federal Circuit, "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), *citing Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), and *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Indeed, the Court recognized that a considerable amount of experimentation may be required, so long as it does not amount to undue experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id., citing In re Jackson*, 217 USPQ 804 (Bd. App. 1982). Applicants respectfully submit that the production and screening of the claimed compounds would require merely routine, and not undue, experimentation, given the relative skill of those in the art and the guidance provided by the specification. Applicants submit that the skilled artisan is well-versed in the production of monoclonal antibodies, for example, using well-established and widely available techniques. In addition, Applicants submit that the screening of such antibodies and other compounds, such as polypeptides or small organic molecules, similarly requires merely routine testing using well-known methods, such as those described throughout the specification and above. Accordingly, Applicants respectfully submit that the pending claims satisfy the enablement requirement of §112 and request that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 19 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse these bases of rejection and submit that the instant claims particularly point out and distinctly claim the subject matter of the invention, as required by Section 112, second paragraph. Applicants specifically address each basis of rejection below.

First, the Action alleges that the claims are indefinite because they are directed to a vitamin B12 binding site on TcII, but the specification does not teach the location of any such binding site, so the metes and bounds of agents directed to the site cannot be readily ascertained.

Applicants respectfully submit that claim 1 has been amended, without acquiescence and solely to expedite prosecution, and no longer explicitly require that the growth blocking agent is directed to a vitamin B12 binding site on TcII. Applicants further submit that this amendment obviates this basis of rejection.

Furthermore, the Action alleges the term "small" in claim 2 is indefinite. Applicants respectfully submit that the term "small organic molecule" is a term of art widely used and understood by the skilled artisan. Accordingly, Applicants submit that the skilled artisan would be apprised as to the scope of the claimed invention, and, therefore, the claim is not indefinite.

The Action also alleges that the meaning of "antagonizing or modulating said binding site" in claim 1 is unclear. Applicants traverse this basis of rejection and submit that the skilled artisan would clearly understand these terms, particularly in light of the definitions provided by the instant specification, which defines both competitive antagonists and modulating agents on page 7, lines 20-27. Competitive antagonists are defined as agents which competitively bind to (or sterically hinder) a B12/TcII receptor or a binding site, thereby inhibiting cellular uptake of vitamin B12. Modulating agents are defined as agents which bind to a B12/TcII receptor or a binding site, and result in the clearing or removal of a B12/TcII receptor or a B12/TcII complex for a period of time (generally hours). Nonetheless, Applicants note that these terms have been removed from claim 1, thereby obviating this basis of rejection.

The Action objects to the Markush group of claim 2 as improper. Without acquiescing to this basis of rejection, Applicants have amended claim 2 so that it no longer contains a Markush group, thereby obviating this basis of rejection.

The Action objects to claim 19 as depending upon cancelled claims. Applicants have amended claim 19 to depend from pending claims 1-4, thereby obviating this basis of rejection.

In light of these amendments and remarks Applicants respectfully submit that the pending claims satisfy the second paragraph requirements of §112 and request that these grounds of rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-4 and 19 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Marcoullis *et al.* (*British Journal of Haematology 43(1)*:15-26,1979). More specifically, the Action alleges that Marcoullis *et al.* teach IgG blocking antibodies that neutralized the total unsaturated vitamin B12 binding capacity, suggesting that the antibodies contained blocking antibodies against transcobalamins. The Action further asserts that these antibodies necessarily possess the functions recited in the claims.

Applicants respectfully traverse this basis of rejection and submit that Marcoullis *et al.* fails to teach each element of the claimed invention and, therefore, does not anticipate the claimed invention. As a first matter, Applicants note that claim 2, as amended, is directed to small organic molecules and, therefore, is clearly not anticipated by the cited antibodies, which are not small organic molecules. Regarding claims 1, 3, 4, and 19, Applicants respectfully submit that the cited reference fails to disclose isolated antibodies directed to TcII. Instead, Marcoullis *et al.* describe an IgM fraction derived from a patient, which necessarily includes a large number of different antibodies, many or most of which are not directed against transcobalamin. Marcoullis *et al.* also do not describe antibody derivatives. In addition, claim 21 is directed specifically to monoclonal antibodies and, therefore, is not anticipated by the polyclonal antibodies described in Marcoullis *et al.* Support for claim 21 is provided throughout the specification as originally filed, including, for example, Examples 9-15, which describe the preparation, purification, and identification of monoclonal antibodies that inhibit cellular uptake of vitamin B_{12}. Accordingly, Applicants respectfully submit that Marcoullis *et al.* does not teach each element of the claims and, therefore, cannot anticipate the instant claims.

Claims 1, 2 and 19 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Shimizu *et al.* (*Oncology 44(3)*:169-173, 1987). Specifically, the Action alleges that Shimizu *et al.* teaches the compound, methyl-B_{12}, which has an antitumor effect. The Action therefore concludes that methyl-B_{12} meets the claimed structural and functional limitations of a claimed small organic molecule.

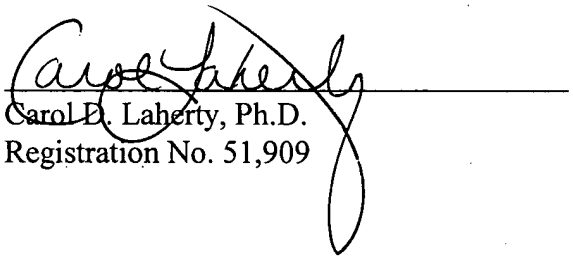
Applicants respectfully traverse this basis of rejection and submit that Shimizu *et al.* fails to teach each element of the claimed invention. Applicants first note that methyl-B_{12} is not a polypeptide or antibody, as recognized by the Action, and, therefore, clearly does not anticipate claims 3, 5, or 21, which are directed to polypeptides, antibodies, and monoclonal

antibodies, respectively. Applicants also submit that Shimizu *et al.* fails to teach or describe a compound capable of inhibiting the cellular uptake of vitamin B_{12} and provides no evidence that methyl-B_{12} is directed to TcII. Rather, Shimizu *et al.* merely shows that methyl-B_{12} is capable of exerting an antitumor effect by stimulating the immune response, as demonstrated by methyl-B12 promotion of mitogen-stimulated splenic lymphocyte blastoformation. Shimizu *et al.* fails to teach or even suggest that the observed anti-tumor effect may be related to methyl-B_{12} inhibiting cellular uptake of vitamin B_{12}. Accordingly, Applicants respectfully submit that Shimizu *et al.* does not teach each element of the claims and, therefore, cannot anticipate the instant claims. In light of these remarks, Applicants respectfully request that the rejections under § 102(b) be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

In view of the above amendments and remarks, allowance of the pending claims is respectfully requested. A good faith effort has been made to place this application in condition for allowance. However, should the Examiner have any questions prior to allowance, the Examiner is requested to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,
A. Charles Morgan, Jr. et al.
Seed Intellectual Property Law Group PLLC



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The title has been amended as follows:

~~GROWTH BLOCKING AGENTS~~ COMPOUNDS THAT INHIBIT VITAMIN B12 UPTAKE

The paragraph beginning at line 6 of page 1 has been amended as follows:

This application is a continuation of U.S. Patent Application Serial No. 08/584,959, filed January 11, 1996, now abandoned, which is a continuation-in-part of ~~claims priority from~~ U.S. Patent Application Serial No. 08/476,440, filed June 7, 1995, now abandoned, which is a continuation-in-part of U.S. Patent Application Serial No. 08/381,522, filed January 31, 1995, now abandoned, which is a continuation-in-part of U.S. Patent Application Serial No. 08/306,504, filed September 13, 1994 and issued as U.S. Patent No. 5,688,504 on November 18, 1997, which is a continuation-in-part of U.S. Patent Application Serial No. 07/880,540, filed May 8, 1992, now abandoned.

In the Claims:

Claims 1-4 and 19 have been amended as follows:

1. (Amended) An isolated growth blocking agent directed to ~~a vitamin B_{12} binding site on~~ TcII, said agent being capable of ~~competitively antagonizing or modulating said binding site to~~ inhibiting the cellular uptake of vitamin B_{12}.

2. (Amended) The agent of claim 1 wherein said agent is ~~selected from the group consisting of proteins, peptides and~~a small organic molecules.

3. (Amended) The agent of claim ~~2~~ 1 wherein said agent is a protein or peptide.

4. (Amended) The agent of claim 3 wherein said agent is an antibody or antibody derivative.

19. (Amended) A pharmaceutical composition comprising a growth blocking agent according to any one of claims 1-~~15~~ 4 and a pharmaceutically acceptable carrier or diluent.

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